

RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF LOBEGLITAZONE SULPHATE IN ORAL THIN FILM FORMULATION

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ABSTRACT:

The present study aimed to develop, evaluate, and analytically validate oral thin films (OTFs) containing Lobeglitazone Sulphate for the management of type 2 diabetes mellitus. OTFs were prepared by the solvent casting technique using hydroxypropyl methylcellulose (HPMC E5) and hydroxypropyl cellulose (HPC) as film-forming polymers. The prepared films were evaluated for physicochemical and mechanical properties, including thickness, weight variation, folding endurance, tensile strength, surface pH, disintegration time, drug content uniformity, and in vitro drug release. Among the developed formulations, batch F5 exhibited the most desirable performance, showing uniform thickness (0.25 ± 0.02 mm), high folding endurance (167 ± 6), rapid disintegration (32.6 ± 0.24 s), satisfactory drug content ($95.70 \pm 0.10\%$), and maximum cumulative drug release (94.97% within 30 min). Accelerated stability studies conducted at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH for 60 days confirmed the stability of the optimized formulation. An RP-HPLC method was also developed and validated for the quantitative estimation of Lobeglitazone Sulphate in OTFs. The method demonstrated excellent linearity over the concentration range of 3.12 – 100 $\mu\text{g/mL}$ ($R^2 = 0.9997$) and complied with ICH validation guidelines. The study concludes that Lobeglitazone Sulphate OTFs represent a promising patient-friendly drug delivery system with reliable analytical quality control.

Keywords: Lobeglitazone Sulphate; Oral thin films; Solvent casting; RP-HPLC; Type 2 diabetes mellitus

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INTRODUCTION:

The oral route remains the most widely used route of drug administration due to its convenience and patient acceptability. However, solid dosage forms like tablets and capsules are often difficult for elderly and pediatric patients, and those with dysphagia. First-pass hepatic metabolism can also limit bioavailability, and conventional formulations may act slowly. Oral thin films (OTFs) have emerged as a patient-friendly alternative, dissolving rapidly in saliva to enable mucosal absorption without water, bypassing first-pass metabolism, and offering faster onset of action than tablets¹⁻².

OTFs disperse the active drug uniformly within a polymeric matrix. Upon contact with the tongue or buccal mucosa, the film hydrates and disintegrates quickly, eliminating the need for swallowing and offering accurate dosing, better adherence, and convenience where water access is limited³⁻⁴. Among fabrication methods, solvent casting is preferred for its simplicity, cost-effectiveness, and ability to produce films with uniform drug distribution and consistent thickness. Formulating OTFs typically involves film-forming polymers, plasticizers, saliva stimulants, superdisintegrants, and other excipients that determine the film's strength and drug release behavior⁵⁻⁶. Type 2 diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycemia due to

impaired insulin secretion, reduced insulin sensitivity, or both⁷. Lobeglitazone Sulphate, a thiazolidinedione, acts as a selective PPAR- γ agonist that improves peripheral insulin sensitivity and glucose uptake. Clinical evidence shows it effectively lowers fasting glucose and HbA1c while improving lipid and hepatic parameters, making it a valuable agent for type 2 diabetes therapy⁸.

A thorough assessment of the existing scientific literature revealed a notable absence of any validated reversed-phase high-performance liquid chromatographic (RP-HPLC) analytical procedure specifically designed for the quantitative determination of Lobeglitazone within OTF dosage forms. Accordingly, the present research was undertaken to develop and validate a precise, sensitive, and reproducible RP-HPLC method compliant with ICH Q2(R1) analytical validation guidelines for the accurate assay of Lobeglitazone. Moreover, no commercially available oral thin film (OTF) formulation containing Lobeglitazone has been reported to date. Motivated by this identified gap, the present study aimed to formulate and optimize Lobeglitazone-loaded oral thin films using pharmaceutical-grade polymeric excipients. The developed films were subjected to comprehensive physicochemical evaluation, including assessment of drug content and in vitro

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drug release characteristics, to determine their overall quality and performance.

MATERIALS AND METHODS:

Materials:

Lobeglitazone Sulphate was provided as a gift sample by Glenmark Pharmaceuticals Ltd., Nashik, India. Hydroxypropyl methylcellulose (HPMC E5), utilized as a primary film-forming polymer, was acquired from Loba Chemie Pvt. Ltd., Mumbai, India. Hydroxypropyl cellulose (HPC), employed as an auxiliary polymer, was sourced from Deepak Cellulose Pvt. Ltd., Gujarat, India. All other excipients used in the formulation work were of analytical reagent grade and were procured from S.D. Fine Chemicals, Mumbai, India. HPLC-grade solvents comprising ammonium acetate, methanol, acetonitrile, and high-purity water were obtained from Merck Ltd., Mumbai, India.

Methods:

Preformulation Study:

Organoleptic Evaluation:

The organoleptic properties of the drug, including color and odor, were evaluated and recorded.

Determination of melting point:

The melting point of Lobeglitazone Sulphate was determined by the capillary tube method. A small quantity of the drug was introduced into a capillary tube sealed at one end and placed in a melting point apparatus. The temperature at which complete melting of the sample occurred was recorded as the melting point of the drug⁹.

Determination of solubility of drug:

The dissolution behaviour of Lobeglitazone Sulphate was investigated across a range of commonly used pharmaceutical solvents, including methanol, ethanol, acetone, dimethyl sulfoxide (DMSO), and purified water. The solubility findings were systematically recorded to identify a compatible solvent system for subsequent formulation preparation and analytical method development⁹.

Standard Graph for Lobeglitazone:

UV-visible spectrophotometric scanning was employed to establish the wavelength of maximum absorbance (λ_{max}) of Lobeglitazone Sulphate. A precisely weighed quantity of the drug (10 mg) was dissolved in methanol and the volume was made up to 100 mL to yield the primary stock solution. This stock solution was further diluted to attain a final concentration of 10 $\mu\text{g/mL}$. The solution was subjected to wavelength scanning over the range of 200–400 nm using methanol as a blank, and the absorption spectrum was recorded to determine the λ_{max} value¹⁰.

Determination of Calibration Curve:

A calibration curve for Lobeglitazone Sulphate was established using a double-beam UV-Visible spectrophotometer. Standard solutions in the concentration range of 2–10 $\mu\text{g/mL}$ were prepared using methanol as the solvent. The absorbance of each solution was measured at 217 nm against methanol as the reference blank. A calibration

curve of absorbance versus concentration was plotted and the data were subjected to linear regression analysis¹¹.

FT-IR Drug -Excipient Compatibility Studies:

Physicochemical compatibility between Lobeglitazone Sulphate and the selected formulation excipients was evaluated using Fourier Transform Infrared (FTIR) spectroscopy. The pure drug and physical drug-excipient mixtures were analysed using the potassium bromide (KBr) disc technique. The resulting infrared spectra were carefully examined for any notable alterations in the characteristic functional group absorption bands of the drug, which might signal incompatibility or chemical interactions between the drug and excipients¹².

Preparation of oral films:

Lobeglitazone Sulphate-loaded oral thin films were fabricated employing the solvent casting technique. Accurately measured quantities of HPMC E5 and hydroxypropyl cellulose were dissolved in purified water under continuous mechanical stirring to yield a clear, homogeneous polymeric solution. In a separate beaker, Lobeglitazone Sulphate was dissolved in ethanol, and this drug solution was gradually added to the polymeric solution with continuous stirring. Propylene glycol was incorporated as a plasticizing agent to impart flexibility to the film matrix, while citric acid was added to function as a saliva-stimulating excipient. The resultant solution was stirred uniformly to achieve complete dissolution and homogeneous dispersion of all components. Entrapped air bubbles within the casting solution were eliminated by either sonication or by allowing the solution to rest undisturbed. The degassed solution was uniformly poured into glass Petri dishes and allowed to dry under ambient room temperature conditions for 24 hours. Following complete desiccation, the resulting films were gently detached and cut into uniform rectangular strips of $2 \times 2 \text{ cm}^2$ dimensions for subsequent evaluation studies.

Table 1: Composition of Lobeglitazone Sulphate Oral Thin Film Formulation Batches (F1–F9)

S	Ingred	F	F	F	F	F	F	F	F
r	ient	1	2	3	4	5	6	7	8
.									
N									
o									
1	Lobegl	5	5	5	5	5	5	5	5
	itazone	.	.	.	.	.	.	.	.
	Sulpha	5	5	5	5	5	5	5	5
	te (mg)								

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2	HPMC	1	1	1	2	2	2	2	2	2
	E5	5	5	5	0	0	0	5	5	5
	(mg)	0	0	0	0	0	0	0	0	0
4	Hydro	5	1	1	5	1	1	5	1	1
	xyprop	0	0	5	0	0	5	0	0	5
	yl		0	0		0	0		0	0
	cellulo									
	se									
	(mg)									
5	Propyl	1	1	1	1	1	1	1	1	1
	ene									
	glycol									
6	Citric	1	1	1	1	1	1	1	1	1
	acid	0	0	0	0	0	0	0	0	0
	(mg)									
7	Ethano	3	3	3	3	3	3	3	3	3
	l									
8	Water	7	7	7	7	7	7	7	7	7

Dose calculations:

Petri dish diameter: 7.5cm (Radius =3.75cm)

Casting Area: $3.14 \times (3.75)^2 = 44.18 \text{cm}^2$

Film Size = 4cm^2

Lobeglitazone dose = 0.5mg

Total no of film get from petri dish = $44.18 \div 4 = 11.45$

Total drug required petri dish = $11 \times 0.5 = 5.5 \text{mg}$

Evaluation of Oral Film:

Thickness:

Thickness measurements of the prepared films were recorded at multiple randomly selected points across each film strip using a calibrated digital Vernier caliper or micrometer screw gauge. The uniformity of film thickness across different positions was used to assess the consistency of the casting process¹³⁻¹⁴.

Weight variation:

A total ten film strips were randomly withdrawn from each formulation batch and individually weighed on an analytical balance. The mean film weight was computed, and the deviation of each individual strip weight from the batch mean was determined. This analysis was conducted to confirm uniform weight distribution among films within the same batch¹³⁻¹⁴.

Folding endurance:

The mechanical resilience of the prepared films was quantified by subjecting each strip to a repeated folding test. Individual film strips were successively folded at the identical crease point until visible cracking or rupture was observed. The

cumulative number of folds endured prior to failure was recorded as the folding endurance value and served as an indicator of the film's overall mechanical integrity¹³⁻¹⁴.

Tensile strength:

Tensile strength denotes the maximum mechanical stress that a film specimen can withstand at the point of breaks. It was quantified using the following formula¹³⁻¹⁴.

Tensile Strength = Force at break / (Thickness × Width)

Surface pH:

To determine the surface pH, an individual film was dissolved in 10 mL of distilled water and the pH of the resulting solution was measured using a calibrated pH meter¹³⁻¹⁴.

Disintegration test:

The in vitro disintegration behaviour of the oral thin films was assessed by placing each strip in a Petri dish containing 10 mL of distilled water maintained at ambient temperature. The dish was gently agitated manually at 10-second intervals, and the time elapsed until the onset of film fragmentation or complete disintegration was recorded as the disintegration time¹³⁻¹⁴.

In-vitro drug release:

Drug dissolution studies were conducted using USP dissolution apparatus type II (paddle configuration). Phosphate buffer (pH 6.8, 250 mL) maintained at $37 \pm 0.5^\circ\text{C}$ served as the dissolution medium, with a paddle rotation speed of 50 rpm. Each film strip was affixed to a glass disc with an appropriate adhesive and positioned at the base of the dissolution vessel with the film surface facing upward. Aliquots of 5 mL were withdrawn at predefined time intervals and replaced with equivalent volumes of fresh phosphate buffer (pH 6.8) to maintain sink conditions. The withdrawn samples were filtered through Whatman filter paper (0.45 µm pore size), suitably diluted, and quantified spectrophotometrically at 217 nm using a UV-visible spectrophotometer¹⁵.

Drug Content Uniformity:

The drug content of the prepared films was determined by dissolving a precisely cut film specimen of 4 cm² surface area in 100 mL of phosphate buffer (pH 6.8) with continuous stirring. The resulting solution was passed through Whatman filter paper, and the absorbance of the filtrate was measured at 217 nm using a UV-visible spectrophotometer. The drug content was subsequently calculated from the measured absorbance values¹⁴.

Stability Studies:

Accelerated stability evaluation of the optimized film formulation was conducted in compliance with ICH guidelines for pharmaceutical products. The films were stored under controlled conditions of $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ relative humidity within a thermostatically regulated stability chamber over a duration of 60 days. Samples were retrieved at scheduled intervals and subjected to visual

inspection for physical appearance, as well as quantitative evaluation of disintegration time, folding endurance, and drug content to monitor any formulation changes during accelerated storage¹⁶.

METHOD DEVELOPMENT AND VALIDATION

Instrumentation:

All chromatographic separations and quantitative analyses were performed on a Shimadzu high-performance liquid chromatography system (model SCL-10AVP), fitted with a binary gradient pump (model LC-10ATVP) and interfaced with data processing software.

Selection of chromatographic mode:

Reversed-phase high-performance liquid chromatography (RP-HPLC) was identified as the preferred analytical technique for the quantification of Lobeglitazone, primarily based on the drug's moderate lipophilicity and suitability for non-polar stationary phases. RP-HPLC offers reliable quantitative accuracy, good peak resolution, and practical run times. The use of a hydrophobic stationary phase in conjunction with a relatively hydrophilic mobile phase was considered optimal for achieving efficient and reproducible chromatographic separation of the analyte.

Selection of Stationary Phase:

A Zodiac C18 analytical column (5 μ m particle size, 150 $\times$ 4.6 mm internal diameter) was employed as the stationary phase throughout the method development and validation.

Selection of Mobile phase:

Multiple mobile phase compositions were systematically screened to identify an optimal chromatographic system providing satisfactory peak resolution, symmetry, and retention characteristics. Various binary combinations including formic acid/acetonitrile and ammonium acetate/acetonitrile were evaluated under both isocratic and gradient elution modes. Prior to injection, all mobile phase solutions were ultrasonicated and passed through 0.45 μ m membrane filters to remove air bubble. Among the systems investigated, a binary mixture comprising 15 mM ammonium acetate buffer and acetonitrile at a ratio of 53:47 (% v/v) under isocratic conditions yielded a well-resolved, symmetrical peak with acceptable retention time and tailing characteristics. This composition was consequently selected for all subsequent analyses.

Preparation of Sample:

Exactly 6 mg of Lobeglitazone was accurately weighed and dissolved in 6 mL of an acetonitrile-methanol-water solvent system (2:3:1, v/v/v) to prepare a primary stock solution at a concentration of 1000 μ g/mL (1000 ppm). The solution was ultrasonicated for 3–5 minutes to ensure complete dissolution. A blank solution was identically prepared using the same mixture. From this blank, 0.6 mL was discarded and replaced with an equal volume of the prepared stock solution. The resulting mixture was thoroughly vortexed to

achieve a final working concentration of 100 μ g/mL (100 ppm) and sonicated briefly prior to injection if required.

Selection of Flow Rate:

Various flow rates of the mobile phase were investigated during method development. The flow rate that yielded the highest column efficiency (expressed as theoretical plate count, N) combined with optimal peak resolution and an acceptably short analysis time was selected as the operational flow rate.

METHOD VALIDATION:

The developed RP-HPLC method was validated in accordance with the ICH Q2(R1) guideline on validation of analytical procedures. The following validation parameters were assessed: repeatability, intraday and interday precision, specificity, system suitability, robustness, linearity, accuracy, limit of detection (LOD), and limit of quantification (LOQ). These studies collectively established the performance characteristics and suitability of the analytical procedure for routine estimation of Lobeglitazone in pharmaceutical formulations.

Repeatability:

The repeatability of the analytical method was evaluated by injecting a freshly prepared Lobeglitazone standard solution at a concentration of 100 ppm for six consecutive injections under identical chromatographic conditions. Analytical repeatability was expressed as the percentage relative standard deviation (%RSD) of the corresponding peak areas obtained across all injections¹⁷.

Precision:

Precision was assessed through two complementary experimental approaches: intraday precision and interday precision. Intraday precision was established by performing three replicate analyses of the test solution (100 ppm) within a single analytical session. Interday precision was evaluated by repeating the analysis on three non-consecutive days over a defined study period. In both cases, precision was reported as %RSD, and values not exceeding 2.0% were considered indicative of satisfactory method precision¹⁷.

Specificity:

The method's specificity was proven when it was recorded and compared that there was no interference between the test sample and the standard. The tailing factor (T), resolution factor (Rs), and retention time (R) were examined¹⁸.

System suitability:

System suitability was verified prior to each analytical run by injecting the Lobeglitazone standard solution (100 ppm) six times consecutively. Chromatographic performance parameters including peak area, theoretical plate count (N), tailing factor, and resolution were monitored to confirm that the HPLC system was functioning within acceptable performance criteria¹⁹.

Robustness:

The robustness of the validated method was assessed by deliberately introducing controlled minor perturbations to the optimized chromatographic conditions. The variables modified included the mobile phase flow rate (± 0.1 mL/min), acetonitrile proportion in the mobile phase ($\pm 2\%$ v/v), and UV detection wavelength (± 2 nm). The impact of these deliberate variations on the chromatographic response was monitored to determine the resilience of the method to minor operational changes encountered during routine laboratory use²⁰

Linearity:

Linearity was established by analyzing Lobeglitazone standard solutions over the concentration range of 3.12–100 ppm. A calibration curve was constructed by plotting peak area against concentration, and the correlation coefficient (R^2) was calculated to determine the degree of linear relationship between the analytical response and drug concentration²⁰.

Accuracy:

Accuracy of the proposed method was determined using recovery studies at three concentration levels corresponding to 80%, 100%, and 120% of the target concentration (100 μ g/mL). Known quantities of Lobeglitazone standard were added to previously analyzed formulation samples, and the percentage recovery was calculated to evaluate the accuracy of the method.

Limit of detection (LOD):

The limit of detection represents the lowest concentration of analyte that can be detected but not necessarily quantified with acceptable accuracy. The LOD value was calculated using the formula²⁰

$$\text{LOD} = 3.3\sigma / S$$

Limit of Quantification (LOQ):

The limit of quantification is defined as the minimum concentration of analyte that can be quantified accurately and precisely under the established conditions. The LOQ was calculated using the formula²⁰.

$$\text{LOQ} = 10\sigma / S$$

RESULTS AND

DISCUSSION:

PREFORMULATION STUDIES:

Organoleptic Characteristics:

Colour: White to off-white solid

Odour: Odourless

Determination of melting point:

The experimentally determined melting point of Lobeglitazone Sulphate was recorded at 166°C, which falls within the reference interval of 165–167°C as documented in the literature. The reported values confirms the identity and chemical purity of the drug substance received, indicating the absence

of any significant contaminants that would otherwise alter the melting behaviour.

Determination of solubility of drug:

Solubility profiling demonstrated that Lobeglitazone Sulphate exhibited practically insoluble in water under ambient conditions. In contrast, the drug displayed considerably higher solubility in organic solvents, particularly methanol, ethanol, and dimethyl sulfoxide (DMSO), which were identified as suitable solvent candidates for formulation development and analytical applications.

Determination of λ max of Lobeglitazone:

The λ -max of Lobeglitazone Sulphate was taken UV-visible Spectrophotometer (Shimadzu, UV-1800 Japan) by Scanning a diluted solution that was prepared in concentration range of 10 μ g/mL and analyzed the solution and absorbance was taken. The λ -max of Lobeglitazone Sulphate was found to be 217 nm.

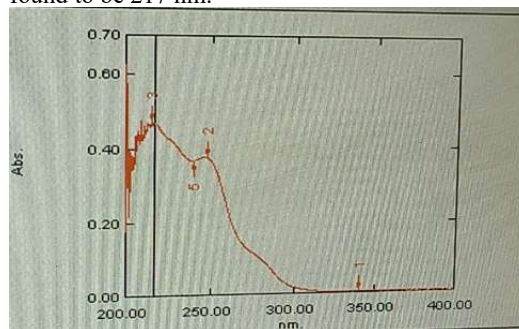


Figure 1: UV Absorption Spectrum of Lobeglitazone Sulphate

Calibration curve for Lobeglitazone:

Preparation of Calibration curve for Lobeglitazone:

The calibration curve of lobeglitazone was drawn by measuring the absorbance of different concentrations in methanol at 217 nm. The calibration curve obtained is shown in Table 2 and Figure 2.

Table No.2 : Calibration curve of Lobeglitazone sulphate

Sr. No	Concentration (μ g/ml)	Absorbance (217nm)
1	2	0.15
2	4	0.24
3	6	0.32
4	8	0.40
5	10	0.47

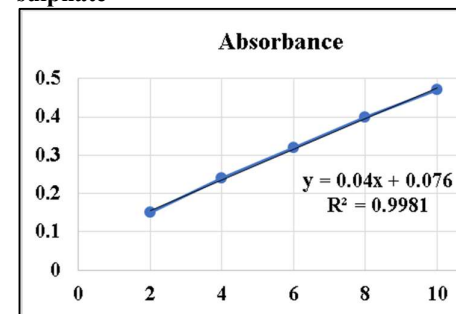


Figure No. 2: Calibration curve of Lobeglitazone Sulphate

The calibration data exhibited a linear relationship over the concentration range studied, consistent with Beer-Lambert's law. A correlation coefficient (R^2) of 0.998 was obtained, confirming excellent linearity of the analytical response for Lobeglitazone Sulphate across the tested concentration range.

FT-IR Drug – excipient compatibility studies:

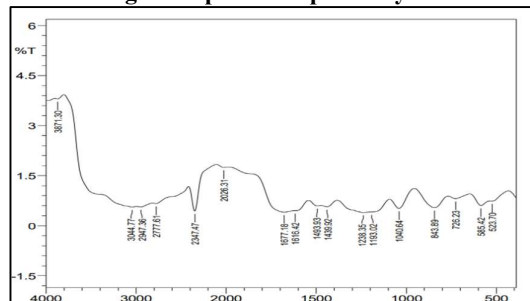


Figure No.3: FTIR Spectra of Lobeglitazone

FTIR spectroscopic analysis of the pure Lobeglitazone Sulphate revealed a set of characteristic absorption bands corresponding to the drug's structural functional groups. A prominent carbonyl (C=O) stretching vibration was recorded at approximately 1677 cm^{-1} . Aromatic ring C=C stretching vibrations appeared at 1616 cm^{-1} and 1493 cm^{-1} , while the band at 3044 cm^{-1} was attributed to aromatic C-H stretching. Additional absorption features corresponding to C-N, C-O, and C-S functional groups were also identified, collectively confirming the structural integrity of the compound.

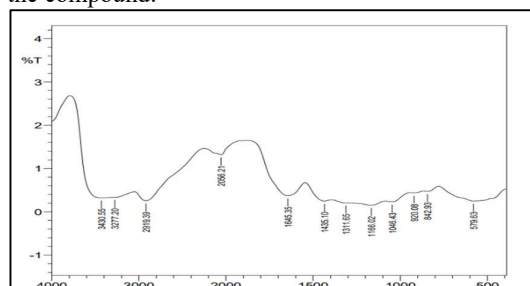


Figure No.4: FTIR Spectra of Lobeglitazone + Polymer

In the FTIR spectrum of the physical drug-polymer mixture comprising Lobeglitazone Sulphate, HPMC E5, and HPC, all the characteristic absorption signals of the drug were retained without any notable shifts or intensity reductions. The predominant C=O stretching band remained at its original wavenumber, confirming the chemical integrity of the drug within the mixture. Broad absorption bands appearing in the $3277\text{--}3430\text{ cm}^{-1}$ region were ascribed to hydroxyl (O-H) stretching vibrations inherent to the polymeric excipients. The preservation of drug-specific spectral features in the binary mixture provided conclusive evidence of the absence of any adverse physicochemical interactions between Lobeglitazone Sulphate and the selected polymer system, thus confirming mutual compatibility.

Evaluation Of Oral Film:

Organoleptic Evaluation of oral film:

Shape - Circular

Odor - Odourless

Colour - Colourless

Weight Uniformity:

The weight of the prepared oral thin films was found to vary between $25.6 \pm 1.2\text{ mg}$ (F1) and $42.8 \pm 1.9\text{ mg}$ (F9). An increase in film weight was observed with increasing polymer content, which can be attributed to the greater amount of solid material incorporated into the film matrix. The relatively low standard deviation values obtained for all formulations indicate uniform film casting and consistent distribution of the drug throughout the films.

Thickness:

Film thickness is a critical quality attribute that influences both drug release kinetics and the mechanical performance of the dosage form. The measured thickness values ranged between $0.15 \pm 0.02\text{ mm}$ (F1) and $0.32 \pm 0.04\text{ mm}$ (F9), with higher polymer concentrations yielding thicker films due to the formation of denser polymeric networks. Formulation F5 showed moderate, reproducible thickness with minimal inter-measurement variability, and all formulations fell within acceptable thickness ranges for OTF dosage forms.

Folding Endurance:

Folding endurance values for the nine formulations ranged from 118 ± 7 (F1) to 174 ± 7 (F9). Formulations with higher polymer concentrations exhibited improved mechanical flexibility and resistance to fracture under repeated stress, consistent with the strengthening effect of the polymeric matrix. Formulation F5 demonstrated notably good folding endurance (167 ± 6), indicating excellent handling properties and resistance to breakage, which are critical for patient-convenient dosage forms.

Disintegration Time:

Disintegration time profiles showed a clear dependence on polymer concentration across the formulation range. Batches F1–F3, prepared with lower polymer levels, disintegrated rapidly within 28.5 ± 0.28 to 36.8 ± 0.31 seconds owing to faster water penetration into the less dense film matrix. Formulations F4–F6 showed intermediate disintegration times of 32.6 ± 0.24 to 40.9 ± 0.34 seconds, with F5 exhibiting the best-balanced disintegration behaviour. Batches F7–F9, characterised by the highest polymer concentrations and film thicknesses, showed markedly slower disintegration (38.2 ± 0.29 to 73.1 ± 0.41 seconds) due to the retardation of aqueous medium ingress. Overall, F5 was identified as the optimised formulation, combining rapid disintegration with satisfactory film properties.

Tensile strength:

The tensile strength of lobeglitazone oral thin films was found in the range of 1.73 ± 0.05 to $3.08 \pm$

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0.08 N/mm², indicating that all films had acceptable mechanical strength. F1 showed the lowest tensile strength, which may be due to a weaker polymeric matrix, while F9 showed the highest value, suggesting greater rigidity due to higher polymer concentration.

Surface pH:

The surface pH of formulations F1–F9 was found to range from 6.57 ± 0.09 to 6.91 ± 0.12 across all batches. These values closely approximate the physiological salivary pH range, suggesting minimal likelihood of oral mucosal irritation following administration. No statistically significant differences in surface pH were observed among the formulation batches, confirming the adequacy of the buffer system employed.

Drug content:

Drug content determinations confirmed a consistent and uniform distribution of Lobeglitazone within all prepared film formulations. Content uniformity values ranged from 90.53 ± 0.40% (F2) to 95.70 ± 0.10% (F5). Formulation F5 yielded the highest drug content with the least variability, signifying efficient drug entrapment and homogeneous dispersion within the HPMC E5–HPC polymeric matrix.

In-vitro Drug Release Study:

Drug release from all OTF formulations (F1–F9) was observed to increase progressively with time. At the 2-minute time point, cumulative drug release ranged from 2.50% to 10.00%, rising to between 75.75% and 94.97% at the 30-minute endpoint. Formulation F5 achieved the highest cumulative drug release of 94.97% at 30 minutes, followed by F4 (92.38%) and F1 (91.19%). The superior release profile of F5 was attributed to its optimised polymer ratio, enhanced hydration kinetics, and faster film disintegration. Formulation F9 exhibited the slowest drug release (75.75% at 30 minutes), consistent with the retardant effect of its higher polymer concentration on drug diffusion. Based on

Formula tion Batches	Physical Appeara nce	Weig ht Film	Thickn ess (mm)	Folding Endura nce
F1	Transpar ent	25.6 ± 1.2	0.15 ± 0.02	118 ± 7
F2	Transpar ent	28.2 ± 1.5	0.19 ± 0.03	134 ± 8
F3	Transpar ent	35.8 ± 1.4	0.22 ± 0.03	128 ± 6
F4	Transpar ent	32.5 ± 1.6	0.20 ± 0.02	156 ± 7
F5	Transpar ent	35.9 ± 1.3	0.25 ± 0.02	167 ± 6
F6	Transpar ent	39.8 ± 1.7	0.28 ± 0.04	152 ± 8
F7	Transpar ent	36.7 ± 1.5	0.24 ± 0.03	144 ± 7
F8	Transpar ent	41.5 ± 1.8	0.29 ± 0.02	162 ± 6
F9	Transpar ent	42.8 ± 1.9	0.32 ± 0.04	174 ± 7

this profile, F5 was confirmed as the optimal formulation.

Table No.3: Evaluation of All the Formulation Batches

All value are expressed as means± Standard Deviation, n=3

Table No.4: Results of Disintegration time, tensile strength, surface pH, Drug Content

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All value are expressed as means± Standard Deviation, n=3

Table 5: *In Vitro* Drug Release Profile of all Formulations

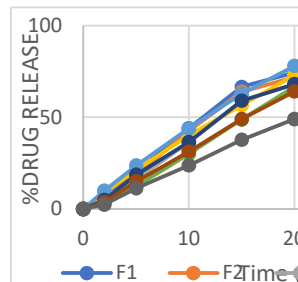


Figure 5: Drug release at different time interval



**Figure 6: Optimize Oral thin Film
Stability Study:
Table 6: Stability Study for optimized F5 Formulation**

Formula tion Batches	Disintegr ation time (Sec)	Tensil e Stren gth (N/m ²)	Surf ace pH	Drug Conten t unifor mity
F1	28.5 ± 0.38	1.73 ± 0.05	6.62 ± 0.07	92.76 ± 0.35
F2	33.6 ± 0.26	1.88 ± 0.07	6.78 ± 0.08	90.53 ± 0.35
F3	37.5 ± 0.31	2.12 ± 0.04	6.74 ± 0.10	94.40 ± 0.30
F4	33.7 ± 0.27	1.91 ± 0.06	6.57 ± 0.09	91.00 ± 0.40
F5	32.6 ± 0.24	2.48 ± 0.05	6.79 ± 0.08	95.70 ± 0.10
F6	40.9 ± 0.34	2.67 ± 0.06	6.82 ± 0.11	94.00 ± 0.40
F7	38.3 ± 0.29	2.73 ± 0.07	6.74 ± 0.09	93.20 ± 0.40
F8	55.6 ± 0.43	2.12 ± 0.04	6.88 ± 0.10	91.10 ± 0.30
F9	73.8 ± 0.41	3.08 ± 0.08	6.91 ± 0.12	94.40 ± 0.40

Per iod (Da ys)	Physic al Appea rance	Thic kness	Disinteg ration Time	Foldi ng Endu rance	Dru g Con tent %	ial	arent	±	0.24	6	0 ±
15	Transp arent	0.25±	33.4±	167 ±	95.4			0.02			0.10
30	Transp arent	0.25±	33.9±	166 ±	95.2			0.01			0.14
Init	Transp	0.25	32.6 ±	167 ±	95.7						

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	arent	0.02	0.12	6	1 ± 0.18
45	Transp arent	0.25± 0.02	34.1± 0.24	165 ± 5	94.9 6 ± 0.16
60	Transp arent	0.25± 0.02	34.7± 0.27	165 ± 7	94.7 2 ± 0.20

All value are expressed as means± Standard Deviation, n=3

The physicochemical stability of the optimised F5 formulation was monitored under accelerated conditions ($40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH) for a 60-day period. Throughout the entire storage duration, the film strips retained their original transparent appearance without any signs of physical deterioration such as cracking, discolouration, or crystalline drug precipitation. Film thickness remained constant at 0.25 mm throughout the study, confirming dimensional stability. A minor but non-significant increase in disintegration time from 32.6 ± 0.24 s (initial) to 34.7 ± 0.27 s (day 60) was noted; however, rapid disintegration was maintained. Folding endurance underwent only a marginal decline from 167 ± 6 to 165 ± 7 , confirming that film flexibility was largely preserved. Drug content exhibited a slight decrease from $95.70 \pm 0.10\%$ to $94.72 \pm 0.20\%$ at day 60, but remained well within the accepted content uniformity limits. These findings collectively establish that the F5 formulation is stable and suitable for storage under ambient conditions.

Method development and Validation:

Selection of wavelength:

The UV absorption spectrum of Lobeglitazone was recorded using a methanolic solution having a concentration of 10 µg/mL. The solution was scanned over the wavelength range of 200–400 nm to identify the wavelength corresponding to maximum absorbance. The highest absorbance was observed at 217 nm (Fig. 6), indicating this wavelength as the λ_{max} of Lobeglitazone. Therefore, 217 nm was selected as the detection wavelength for subsequent RP-HPLC analysis and method validation studies due to its optimum analytical response.

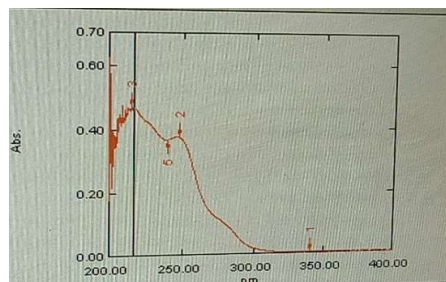


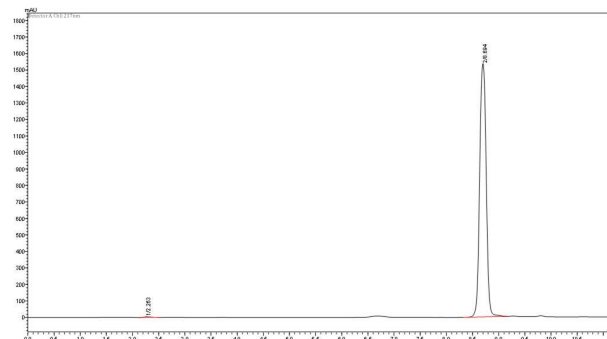
Figure 7: Wavelength of Lobeglitazone at 217 nm.

Method development:

To obtain efficient separation with a short retention time and a sharp, symmetrical peak in accordance with ICH guidelines, several solvent compositions were investigated. The optimization process was also aimed at developing an environmentally friendly analytical method. Among the different chromatographic conditions evaluated, the optimized method was successfully achieved in Trial 4.

Trial

1:



Figure

8 : Trial 1st of lobeglitazone by RP-HPLC

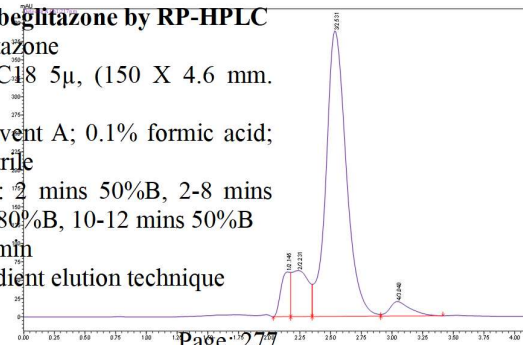
1. Analytes: Lobeglitazone
2. Column: Zodiac C18 5µ, (150 X 4.6 mm. ID.)
3. Mobile Phase: solvent A; 0.1% formic acid; solvent B, acetonitrile
4. Gradient program; 2 mins 30%B, 2-8 mins 80%B, 8-10 mins 80%B, 10-12 mins 30%B
5. Flow rate: 1.0 ml/min
6. Elution mode: gradient elution technique
7. Wavelength selected: 217 nm
8. Temperature: Room temperature

In Trial 1, Lobeglitazone showed a sharp peak at 8.694 min with high area percentage 99.7376% and good tailing factor 1.051. However, the retention time was comparatively longer, so further trials were performed to reduce run time.

Trial 2:

Figure 9: Trial 2nd of lobeglitazone by RP-HPLC

1. Analytes: Lobeglitazone
2. Column: Zodiac C18 5µ, (150 X 4.6 mm. ID.)
3. Mobile Phase: solvent A; 0.1% formic acid; solvent B, acetonitrile
4. Gradient program: 2 mins 50%B, 2-8 mins 80%B, 8-10 mins 80%B, 10-12 mins 50%B
5. Flow rate: 1.0 ml/min
6. Elution mode: gradient elution technique



7. Wavelength selected: 217 nm
8. Temperature: Room temperature
In Trial 2, the Lobeglitazone peak appeared at 2.531 min, showing reduced retention time. However, multiple nearby peaks and low resolution indicated poor separation, so the condition was not selected.

Trial 3:

Figure 10: Trial 3rd of lobeglitazone by RP-HPLC

1. Analytes: Lobeglitazone
2. Column: Zodiac C18 5 μ , (150 X 4.6 mm. ID.)
3. Mobile Phase: 15mM Ammonium acetate -acetonitrile (38:62% v/v)
4. Flow rate: 1.0 ml/min
5. Elution mode: isocratic elution
6. Wavelength selected: 217 nm
7. Temperature: Room temperature

In Trial 3, Lobeglitazone peak was observed at 7.980 min with good peak shape and tailing factor 0.934. But the retention time was again higher, making the method less suitable for routine analysis.

Trial 4 :

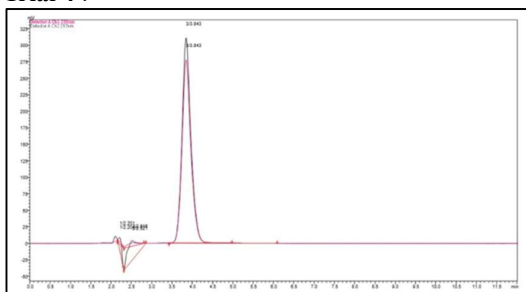


Figure 11: Trial 4 final method development was selected.

1. Analytes: Lobeglitazone
2. Column: Zodiac C18 5 μ , (150 X 4.6 mm. ID.)
3. Mobile Phase: 15 mM ammonium acetate - acetonitrile (53:47% v/v)
4. Flow rate: 1.0 ml/min
5. Elution mode: isocratic elution
6. Wavelength selected: 217 nm
7. Temperature: Room temperature

In Trial 4, Lobeglitazone showed a sharp and well-defined peak at 3.843 min using 15 mM ammonium acetate: acetonitrile. This condition gave suitable retention, acceptable tailing factor, and good separation, so it was selected for further validation

Repeatability:

Repeatability was evaluated from six consecutive injections of a 100 ppm Lobeglitazone standard solution under identical chromatographic conditions. The peak area data and derived statistical parameters are presented in Table 7.

Figure 12: Repeatability studies of Lobeglitazone

Table No.7: Repeatability studies of Lobeglitazone

Sr. No.	Drug Name: Lobeglitazone
	Peak Area; Conc. 100 ppm
1	4750189
2	4615325
3	4608211
4	4711173
5	4704998
6	4689606
Mean	4679917
STD. DEV.	56483.45192
RSD (%)	1.21%

The calculated %RSD of peak areas was 1.21%, which is below the maximum acceptable threshold of 2.0%, confirming the satisfactory repeatability of the developed method.

Specificity Studies:

The specificity study confirmed that the developed RP-HPLC method was capable of specifically detecting Lobeglitazone in the presence of other components. No significant interference was observed at the retention time of Lobeglitazone, indicating that the method was selective, specific, and suitable for accurate analysis of the drug in the developed formulation.

Figure 13: Chromatogram of blank sample

Figure 14: Chromatogram of API of Lobeglitazone

Figure 15: Chromatogram of developed formulation

Precision Studies:

1. Intraday precision

The freshly prepared stock solution of Lobeglitazone of three replicates of same concentrations (100 ppm) were tested and evaluated within the same day (intra-day precision). The %RSD was calculated and found it was less than 2%.

Table No.8: Intraday Precision data of Lobeglitazone

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The results obtained in intraday precision studies was found within 0.24 – 1.10 % which is less than 2%, indicating that the developed RP-HPLC method was precise.

2. Interday precision

The freshly prepared stock solution of Lobeglitazone of three replicates of same concentrations (100 ppm) were tested and evaluated three separate day (inter-day precision). The %RSD was calculated and found it was less than 2%.

Table 9: Interday Precision data of Lobeglitazone

Drug Name: Lobeglitazone				2	100 ppm	998	26	90	0.24						
S. No.	Concentration (ppm)	Area	Average		100 ppm	4689606									
					100 ppm	4737449									
				3	100 ppm	4764684	4738737	25328.06	0.53						
					100 ppm	4714077									
					Range of % RSD					0.24-1.10 %					
				Day	1	4	7	4	5	0	.	5	3		
	100 ppm	764684													
	100 ppm	4714077													
D	100 ppm	4801808	4837354											31388.14	0.65
	100 ppm	4861257													
	100 ppm	4848997													
D	100 ppm	4960464	4963439	16090.56	0.32										
	100 ppm	4949043													
	100 ppm	4980													

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	809			
	Range of % RSD; should be less than 2%			0.32 - 0.65 %

The interday precision study showed %RSD values between 0.32–0.65%, which were below 2%. This indicates that the developed RP-HPLC method is precise.

Robustness Studies:

Robustness of HPLC Method represents its ability to remain unaffected by small but deliberate changes in separation parameters to ascertain its reliability during routine analysis. In this method, robustness was established by making deliberate changes in flow rate (1.0 ± 0.1 ml/mins), organic modifier as solvent B considered as acetonitrile ($\pm 2\%$, v/v), and wavelength (217 ± 2 nm)

Table 10: Robustness data of Lobeglitazone

Variables of robustness	Lobeglitazone			
	Retention time t_R (min)	Ret. factor (k')	Tailoring factor (T_f)	Th. Plates (N)
Flow rate (1.1 ml/min)	3.48	0.84	1.19	2442
Flow rate (0.9 ml/min)	4.2	0.74	1.19	2486
Solvent B composition (49%)	3.46	0.66	1.24	2393
Solvent B composition (45%)	4.3	1.05	1.13	2457
Wavelength 215 nm	3.81	0.74	1.19	2479
Wavelength 219 nm	3.81	0.74	1.19	2476
Average	3.84	0.80	1.19	
Standard deviation	± 0.35	± 0.14	± 0.03	

Linearity Studies:

The linearity of HPLC method represents its ability to explicit the results that should always

proportional to the concentration of studied analytes within a selected range. As observed the selected concentrations of Lobeglitazone (100, 50, 25, 12.5, 6.25 and 3.12 ppm) their peak areas were almost proportional to the specified concentrations. Since in all studies their regression coefficients (R^2) were close to 1 (≈ 0.999). It represents that the developed method has a high degree of linearity.

Table 11: Linearity

data of Lobeglitazone

Name of Drug; Lobeglitazone		
S. No.	Concentration ($\mu\text{g/mL}$)	Area
1	100 $\mu\text{g/mL}$	5040571
2	50 $\mu\text{g/mL}$	2568951
3	25 $\mu\text{g/mL}$	1363298
4	12.5 $\mu\text{g/mL}$	674857
5	6.25 $\mu\text{g/mL}$	344385
6	3.125 $\mu\text{g/mL}$	176192
Regression Equation		$y = 50084x + 51342$
Correlation coefficient (R^2)		0.9997
Std. error of intercept		21160.03546
Std. Dev. Of intercept		51831.28982

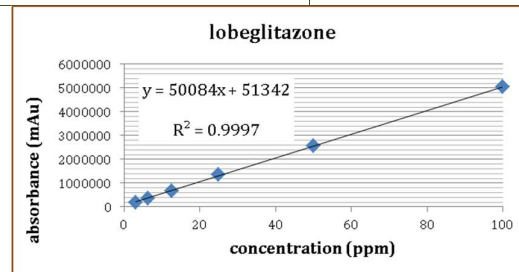


Figure 16: Calibration curve of Lobeglitazone

Accuracy Studies:

The accuracy of the developed RP-HPLC method was evaluated by performing recovery studies at three concentration levels, namely 80%, 100%, and 120% of the target concentration (100 ppm). Each concentration level was analyzed in duplicate by spiking a known quantity of Lobeglitazone standard into the pre-analyzed formulation sample. The percentage recovery of the drug was calculated, and the results are presented in Table 12. The accuracy of the method was further assessed using the calibration curve, where the slope and intercept of the regression equation were utilized to determine the amount of drug recovered from the formulation. The obtained recovery values were found to be within the acceptable limits recommended by ICH guidelines, demonstrating the accuracy of the developed analytical method.

Table 12: Accuracy data of Lobeglitazone

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Drug Name: Lobeglitazone			Drug content : 0.5 mg	Name of Drug: Lobeglitazone							
				Sr. No.	Concentration (µg/mL)	Area					
Standard concentration (%)	Standard (ppm)	Peak area	Drug (%)	Drug (ppm)	1	100 µg/mL	5040571				
					2	50 µg/mL	2568951				
					3	25 µg/mL	1363298				
					4	12.5 µg/mL	674857				
					5	6.25 µg/mL	344385				
					6	3.125 µg/mL	176192				
					Regression Equation		y= 50084x + 51342				
					Correlation coefficient (R ²)		0.9997				
					Std. error of intercept		21160.03546				
					Std. Dev. Of intercept		51831.28982				
100%	100 ppm	461525	804 ppm	Limits of quantification (LOQ)		10.35 µg/mL					
				Limits of detection (LOD)		3.10 µg/mL					
				6.4 ppm	383	3	95				
								6.1 ppm	369	6	84%
				6.4 ppm	383	3	95				
								6.1 ppm	369	6	84%
				6.4 ppm	383	3	95				
								6.1 ppm	369	6	84%
6.8 ppm	390	6	84%								
6.4 ppm	383	3	95								
				6.1 ppm	369	6	84%				
								6.8 ppm	390	6	84%
Drug recovery Range (%) as per ICH = 100±10%		95.84 % - 105.19 %									

LOD and LOQ:

Table No 13: LOD And LOQ Data

System Suitability:

System suitability test included the separation parameters specifically, theoretical plate (N), capacity factor (k'), resolution (R), separation factor (α), tailing factor (T), Mean ± SD and RSD% which should always less than 2% for 6 repetitive injections of same concentration. Table No. 14 displayed the system suitability studies for selected drug, Lobeglitazone.

Table No 14: Represents the System Suitability Studies For Lobeglitazone

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All the parameters of system suitability are observed within specified limit. Hence system suitability is justified.

CONCLUSION:

The present study successfully developed Lobeglitazone Sulphate oral thin films using the solvent casting technique. The prepared formulations exhibited satisfactory physicochemical and mechanical characteristics, including uniform thickness, adequate flexibility, acceptable tensile strength, rapid disintegration behavior, near-neutral surface pH, consistent drug content, and efficient drug release. Among the developed formulations, F5 was identified as the optimized batch based on its superior overall performance. The formulation exhibited an optimum balance between mechanical properties and drug release characteristics, along with rapid disintegration and uniform drug distribution. These findings indicate that the selected combination of polymers and excipients was effective in producing a stable and patient-friendly oral thin film formulation of Lobeglitazone.

In addition, a simple and reliable RP-HPLC method was successfully developed and validated for the quantitative estimation of Lobeglitazone. Validation studies confirmed that the proposed method fulfilled the requirements of ICH guidelines with respect to accuracy, precision, specificity, linearity, robustness, and reproducibility. Therefore, the developed analytical method can be considered suitable for routine quality control, assay determination, and evaluation of Lobeglitazone in oral thin film dosage forms. Overall, the results of the present study suggest that Lobeglitazone-loaded oral thin films represent a promising alternative drug delivery system for the management of type 2 diabetes mellitus and may contribute to improved patient compliance and therapeutic effectiveness.

CONFLICT OF INTEREST:

System suitability parameters	Lobeglitazone	Acceptable Values
Theoretical plates (N)	2469	> 2000
Capacity Factor (K')	0.74	> 1.5 - <10
Selectivity/Separation factor (α)	5.20	> k'
Asymmetry/Tailing factor (T)	1.48	> 2
Retention time (t_R)	3.84 min.	> k'
Wavelength of Detection (nm)	217 nm	> 200 nm
Repeatability (%RSD)	1.21	< 2
Intra-Day Precision (%RSD)	0.24-1.10%	< 2
Inter-Day Precision (%RSD)	0.32 - 0.65%	< 2
Linearity range	3.12 – 100 $\mu\text{g/ml}$	NA
Regression equation	$y = 50084x + 51342$	NA
SE of intercept (S_e)	21160.03546	NA
SD of intercept (S_a)	51831.28982	NA
Correlation Coefficient (r^2)	0.9997	NA
LOQ ($\mu\text{g/mL}$)	10.35 $\mu\text{g/mL}$	NA
LOD ($\mu\text{g/mL}$)	3.10 $\mu\text{g/mL}$	NA

The authors declare that there is no conflict of interest.

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